

An ab initio approach to free-energy reconstruction using logarithmic mean force dynamics

Makoto Nakamura,^{1, a)} Masao Obata,¹ Tetsuya Morishita,² and Tatsuki Oda^{1, 3, b)}

¹⁾ Graduate School of Natural Science and Technology, Kanazawa University, Kanazawa 920-1192, Japan

²⁾ Nanosystem Research Institute, National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba 305-8568, Japan

³⁾ Institute of Science and Engineering, Kanazawa University, Kanazawa 920-1192, Japan

(Dated: 29 May 2014)

We present an *ab initio* approach for evaluating a free energy profile along a reaction coordinate by combining logarithmic mean force dynamics (LogMFD) and first-principles molecular dynamics. The mean force, which is the derivative of the free energy with respect to the reaction coordinate, is estimated using density functional theory (DFT) in the present approach, which is expected to provide an accurate free energy profile along the reaction coordinate. We apply this new method, first-principles LogMFD (FP-LogMFD), to a glycine dipeptide molecule and reconstruct one- and two-dimensional free energy profiles in the framework of DFT. The resultant free energy profile is compared with that obtained by the thermodynamic integration method and by the previous LogMFD calculation using an empirical force-field, showing that FP-LogMFD is a promising method to calculate free energy without empirical force-fields.

Keywords: mean force dynamics, free energy, logarithmic energy potential, glycine dipeptide, 2-(Acetylamino)-N-methylacetamide

I. INTRODUCTION

Free energy is a significant physical property for estimating thermodynamic stability. It is desirable to estimate free energy as accurately as possible. Such free energy estimation is becoming important in a variety of research fields; in particular, biological molecules including proteins or interfaces of nano-scale materials have been raised as a target for free energy calculations¹⁻³. It is thus desirable to develop methods that improve the accuracy and efficiency in free energy calculations using molecular simulation. The free energy in molecular systems has often been evaluated for a given constraint (reaction pass).⁴ Such a constraint is usually specified by using a set of reaction coordinates,⁵ for example, distances between molecules, bond angles, and dihedral angles, etc.

In order to get free energy landscapes, various techniques [thermodynamic integration (TI)⁶, free energy perturbation,⁷ umbrella sampling,⁸ and so on] have been developed so far. Although TI is derived from the statistical mechanics faithfully, some difficulties have been pointed out; poor sampling which could come from a breakdown of the ergodicity and numerical integration as postprocessing.

To overcome these difficulties, free energy calculation methods based on mean force dynamics (MFD) have been proposed.^{9,10} In MFD, a set of L reaction coordinates (collective variables), $\mathbf{X} \equiv \{X_1, X_2, \dots, X_L\}$, is regarded as a set of fictitious dynamical variables, and

their trajectories are designed to be generated by hypothetical dynamical equations. Morishita *et al.*^{11,12} have recently introduced a logarithmic form of the free energy along \mathbf{X} [$F(\mathbf{X})$] to enable us to easily sample rare events in MFD calculations. This method is called logarithmic mean force dynamics (LogMFD), in which the free energy can be estimated on-the-fly.

The evaluation of mean force (MF), i.e., slope of $F(\mathbf{X})$ with respect to \mathbf{X} , in such a method based on MFD can be improved by incorporating first-principles (FP) molecular dynamics (MD),¹³ replacing the classical MD using empirical force fields. FPMD allows us to include effects of the electronic state explicitly; for example, bond-formation or bond-breaking, which may considerably influence the free energy profiles in molecular systems.

In this paper, we have developed first-principles MFD in the framework of LogMFD, namely, first-principles LogMFD (FP-LogMFD). We reconstruct the free energy landscape for a molecular system of glycine dipeptide using FP-LogMFD. This demonstration indicates that FPMD can be incorporated into LogMFD of multi-dimensional \mathbf{X} -systems and that the scheme developed here is found to be promising for the free energy reconstruction using *ab initio* techniques. The successful combination of LogMFD and FPMD is indebted to the efficiency for sampling rare events in LogMFD. The logarithmic form introduced in LogMFD suppresses the effective energy barriers for the dynamical variables \mathbf{X} . This makes it possible to sample configurations with higher energy, as frequently as those with much lower energy. This feature also makes it possible to improve the accuracy of the MF by increasing the number of statistical samples (FPMD steps).

In the next section, we review the LogMFD method

^{a)} Electronic mail: nakamura@cphys.s.kanazawa-u.ac.jp

^{b)} Electronic mail: oda@cphys.s.kanazawa-u.ac.jp

briefly and demonstrate how to incorporate FPMD into LogMFD. In Sec. III, we present the free energy profile with respect to the dihedral angles in glycine dipeptide molecule. In Sec. IV, we will discuss the entropic contribution and numerical accuracy in the present results by comparing it with the classical MD result previously obtained using an empirical force field. Finally, Sec. V summarizes this paper.

II. METHODS

A. Equations of mean force dynamics

We present a brief review for LogMFD. This review would be a good introduction to our new scheme which employs a non-empirical approach. We consider a system of N atoms with a given temperature T_{ext} , and aim to reconstruct the free energy profile $F(\mathbf{X})$ with respect to \mathbf{X} . Each reaction coordinate $X_p(\{\mathbf{R}_I\})$ is generally a function of the atomic coordinates $\{\mathbf{R}_I\}$, where p and I specify the p 'th reaction coordinate and the I 'th atom, respectively. In MFD, however, \mathbf{X} are regarded as dynamical variables, being independent of $\{\mathbf{R}_I\}$. We now consider the following postulated Hamiltonian for \mathbf{X} ;

$$H_{\text{MFD}} = \sum_p^L \frac{1}{2} M_p \dot{X}_p^2 + F(\mathbf{X}), \quad (1)$$

where the first and second terms on the right-hand-side are the kinetic and potential energies, respectively, for X_p (\dot{X}_p means the velocity dX_p/dt) and M_p is the fictitious mass for X_p . The equation of motion for X_p is thus obtained as,

$$M_p \ddot{X}_p = -\frac{\partial F(\mathbf{X})}{\partial X_p}, \quad (2)$$

where $-\partial F(\mathbf{X})/\partial X_p$ is the MF. The solution for this equation of motion fulfills the conservation law, i.e., H_{MFD} can be seen as a constant of motion, as long as the MF is accurately evaluated.

Several methods based on MFD have been proposed thus far, which provide us free energy profiles with respect to reaction coordinates and allow us to discuss many kinds of physics involving the reaction coordinates. Metadynamics¹⁰ has been introduced utilizing the concept of MFD, and has been applied to a variety of systems including biosystems to sample rare events and to reconstruct free energy profiles. Morishita *et al.*^{11,12} have proposed LogMFD in which $F(\mathbf{X})$ in Eq. (1) is replaced with a logarithmic form of $F(\mathbf{X})$, and have demonstrated several improvements in the free energy calculation.

In LogMFD, the following Hamiltonian is introduced instead of Eq. (1);

$$H_{\text{LogMFD}} = \sum_p^L \frac{1}{2} M_p \dot{X}_p^2 + \gamma \log\{\alpha F(\mathbf{X}) + 1\}, \quad (3)$$

where γ and α are positive constant parameters, which are chosen to effectively reduce the energy barriers experienced by \mathbf{X} . The resultant equation of motion for X_p is given as,

$$M_p \ddot{X}_p = -\left(\frac{\alpha\gamma}{\alpha F(\mathbf{X}) + 1}\right) \frac{\partial F(\mathbf{X})}{\partial X_p}. \quad (4)$$

In practice, \mathbf{X} can be thermostatted in LogMFD calculations, and the equation of motion is slightly modified as follows;

$$M_p \ddot{X}_p = -\left(\frac{\alpha\gamma}{\alpha F(\mathbf{X}) + 1}\right) \frac{\partial F(\mathbf{X})}{\partial X_p} - M_p \dot{X}_p \dot{\eta}, \quad (5)$$

$$Q_\eta \ddot{\eta} = \sum_p^L M_p \dot{X}_p^2 - L k_B T_X, \quad (6)$$

where η is the thermostat variable which controls the temperature of \mathbf{X} (T_X), Q_η is the mass for η , and k_B is Boltzmann's constant. With a single Nosé-Hoover thermostat^{14,15} as in Eqs. (5) and (6), the following pseudo Hamiltonian is a constant of motion instead of H_{LogMFD} ;^{11,12}

$$\begin{aligned} \hat{H}_{\text{LogMFD}} = & \sum_p^L \frac{1}{2} M_p \dot{X}_p^2 + \gamma \log\{\alpha F(\mathbf{X}) + 1\} \\ & + \frac{1}{2} Q_\eta \dot{\eta}^2 + L k_B T_X \eta. \end{aligned} \quad (7)$$

Note that T_X is not necessarily the same as the temperature for atoms, T_{ext} . The heights of the energy barriers on $\gamma \log\{\alpha F(\mathbf{X}) + 1\}$ are much lower than those on $F(\mathbf{X})$. This reduction of the barrier height enables the coordinate X_p to easily cross the barriers at a moderate temperature of T_X , allowing us to evaluate the free energy associated with rare events.

$\partial F(\mathbf{X})/\partial X_p$ is obtained as an ensemble average and, practically, can be estimated as a time-averaged quantity from a thermostatted MD or Monte Carlo (MC) simulation at a given temperature T_{ext} with a given potential Φ for the N -atom system and a set of fixed reaction coordinates \mathbf{X} ;

$$\begin{aligned} \frac{\partial F(\mathbf{X})}{\partial X_p} &= \frac{1}{Z} \int d\mathbf{R} \left[\frac{\partial \Phi(\mathbf{R})}{\partial X_p} \right]_{\mathbf{X}} e^{-\Phi(\mathbf{R})/k_B T_{\text{ext}}} \\ &\simeq \frac{1}{\tau} \int_0^\tau dt \left[\frac{\partial \Phi(\mathbf{R}(t))}{\partial X_p} \right]_{\mathbf{X}}, \end{aligned} \quad (8)$$

where

$$Z = \int d\mathbf{R} e^{-\Phi(\mathbf{R})/k_B T_{\text{ext}}}. \quad (9)$$

Here, τ is the simulation time period, and the $[\]_{\mathbf{X}}$ represents the ensemble average under the set of constraints.

In the MF estimation, it is expected that the canonical MD or MC simulation provides the canonical distribution under the constraint on \mathbf{X} . The MF is, in our approach, evaluated using thermostatted FPMD. The potential energy $\Phi(\mathbf{R})$ and the details of the MF evaluation will be discussed later on.

We need to know $F(\mathbf{X})$ to calculate the force on X_p in Eq. (5), however, $F(\mathbf{X})$ itself is the quantity we want to obtain. This problem can be solved using the conserved quantity, H_{LogMFD} or \hat{H}_{LogMFD} [Eq. (3) or (7)]. Using this conservation law, $F(\mathbf{X})$ can be directly evaluated with \hat{H}_{LogMFD} (when we employ a single Nosé-Hoover thermostat) whose value needs to be set at the beginning of the LogMFD run;^{11,12}

$$F(\mathbf{X}) = \frac{1}{\alpha} \left[\exp \left\{ \frac{1}{\gamma} \left(\hat{H}_{\text{LogMFD}} - \sum_p^L \frac{1}{2} M_p \dot{X}_p^2 - \frac{1}{2} Q_\eta \dot{\eta}^2 - L k_B T_X \eta \right) \right\} - 1 \right]. \quad (10)$$

It is required that $F(\mathbf{X}) > 0$ at any \mathbf{X} to enhance the sampling in the \mathbf{X} subspace. This requirement can be actually fulfilled by using appropriate values for \hat{H}_{LogMFD} ; \hat{H}_{LogMFD} should be larger than the sum of the initial kinetic energy for \mathbf{X} and the initial terms for η . See Ref. 12 for details. Equation (10) indicates that the $F(\mathbf{X})$ is successively obtained along the dynamics of $\{X_p\}$, namely, “on-the-fly”. This means that we need not perform any postprocessing unlike in TI, which overcomes some drawbacks of the TI method. In TI, we need to decompose the \mathbf{X} subspace into many bins with a finite width, implying a possible missing of remarkable characters in the free energy due to a discretized mesh. In contrast, LogMFD provides $F(\mathbf{X})$ with much higher resolution than TI, since LogMFD generates almost continuous \mathbf{X} -trajectories and the $F(\mathbf{X})$ trajectories (this will be illustrated in Fig. 6).

Summarizing LogMFD, it allows us to sample higher energy states efficiently and to evaluate the free energy at the local point of reaction coordinates without any postprocessing. The flow chart of the LogMFD method is displayed in Fig. 1. To update $\{X_p\}$, the most important quantity is the MF, which is evaluated using thermostatted FPMD in our approach. Details of our FPMD approach are presented in the next subsection; Car-Parrinello molecular dynamics (CP-FPMD)¹³ with double Nosé-Hoover thermostats.^{16,17}

B. First-principles mean force

In MFD methods, the MF needs to be estimated as accurately as possible at the temperature T_{ext} . The MF from first-principles could improve the accuracy of the free energy profiles. We now address two technical issues associated with the evaluation of the MF in our approach. Firstly, the constraint on \mathbf{X} during the FPMD run is discussed. In order to impose a constraint on atomic coordinates, one may employ the SHAKE method in which

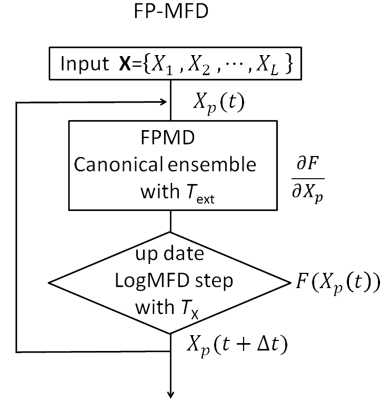


FIG. 1. Flow chart of first-principles LogMFD.

a holonomic constraint is realized,¹⁸ although complex equations should be solved for the Lagrange multiplier. Alternatively, the harmonic potential method can also be utilized, allowing us to use Eq. (8) without any correction terms. In this work, we chose the latter method. Secondly, to keep a given temperature for the system and to generate the canonical distribution for the atomic trajectories, we employ thermostats.

Newly developed thermostats,¹⁹ as well as the original thermostat,^{14,15} can also be used in conjunction with FPMD in which the Born-Oppenheimer(BO) surface is strictly searched in the time evolution²⁰ or CP-FPMD.¹³

In our FPMD approach, the following energy is considered:

$$E_{\text{tot}} = E_{\text{BP}} + E_{\text{hp}}, \quad (11)$$

$$E_{\text{hp}} = \sum_p \frac{1}{2} k_p (\tilde{X}_p(\{\mathbf{R}_I\}) - X_p)^2, \quad (12)$$

$$E_{\text{BP}} = \sum_i m_\varphi \langle \dot{\varphi}_i | \dot{\varphi}_i \rangle + \frac{1}{2} \sum_I M_I \dot{\mathbf{R}}_I^2 + \frac{1}{2} Q_e \dot{x}_e^2 + 2E_{\text{kin}}^0 x_e + \frac{1}{2} Q_R \dot{x}_R^2 + g k_B T x_R + E_{\text{fp}}[\{\varphi_i\}, \{\mathbf{R}_I\}], \quad (13)$$

where E_{BP} and E_{hp} are the energy in the Blöchl-Parrinello(BP) method¹⁶ and the harmonic potentials for the constraint, respectively, and E_{fp} represents the potential energy in the system of electrons and ions (see Eq. (5) in Ref. 16). x_R (x_e) is the dynamical variable for the thermostat and Q_R (Q_e) is the corresponding mass for x_R (x_e). g is the number of ionic degrees of freedom. The quantity $\tilde{X}_p(\{\mathbf{R}_I\})$ in Eq. (12) is constructed from the current atomic coordinates, which is tightly constrained to X_p according to E_{hp} [Eq. (12)]. To this end, the constant k_p is chosen to be a large value. The atomic forces come from the contributions of E_{fp} , the thermostat, and the constraint E_{hp} . These contributions result

in the following equation of motion for \mathbf{R}_I ;

$$M_I \ddot{\mathbf{R}}_I = \mathbf{F}_I^{\text{fp}} - M_I \dot{\mathbf{R}}_I \dot{x}_R - \sum_p k_p (\tilde{X}_p(\{\mathbf{R}_I\}) - X_p) \frac{\partial \tilde{X}_p(\{\mathbf{R}_I\})}{\partial \mathbf{R}_I}. \quad (14)$$

The equations of motion for the wavefunction (φ_i) and the heat baths (x_e and x_R) are not changed from the original BP method by introducing the constraint, implying a less effort for converting a conventional computational code to the present one.

According to Eq. (8), the first-principles mean force is obtained as a time average of $-\partial E_{\text{tot}}/\partial X_p$:

$$-\frac{\partial F(\mathbf{X})}{\partial X_p} \sim k_p \langle \tilde{X}_p(\{\mathbf{R}_I\}) - X_p \rangle, \quad (15)$$

where $\langle \rangle$ represents a canonical ensemble or a time average. This formula is general as far as the atomic configuration samples the canonical distribution under the required constraint. This implies that the relation of Eq. (15) is also useful in the TI method, as explained in Appendix A. In order to show an achievement of the constraint and the temperature control, we present typical time evolution of the reaction coordinate X_p in the next section.

In CP-FPMD, the fictitious kinetic energy of the wave function, namely, the first term in Eq. (13), should follow the dynamics of $\{\mathbf{R}_I\}$ as quickly as possible.¹⁶ To this end, it is important to find an appropriate E_{kin}^0 . For a given atomic configuration, (i) we start a CP-FPMD run with the system exactly on the BO surface. (We converge the electronic state to the BO surface beforehand.) Then (ii) we perform the CP-FPMD run for a few tens of MD steps without the heat baths (may be better, without the constraint). During this period, the system slightly leaves the exact BO surface. (iii) If the temperature of the system reaches T_{st} within the given period, then we set the value of the kinetic energy of the wave functions at the moment as E_{kin}^0 . Due to a practical reason for stabilizing the simulation, T_{st} is taken as $\sim 0.85T_{\text{ext}}$. (iv) When the system does not reach an appropriate temperature, we introduce a new atomic configuration by distorting the previous atomic configuration. We restart the process from (i). After setting E_{kin}^0 , we switch on the thermostats in the BP method accompanied with the constraint of Eq. (12). The rest of the FPMD steps are used for the MF evaluation of Eq. (15). In the computation mentioned above, the initial atomic configurations for each of the series of the CP-FPMD runs were taken from the atomic configuration in the CP-FPMD runs previously done. We will detail the procedure to perform FP-LogMFD calculations, including parameter settings, in the next section.

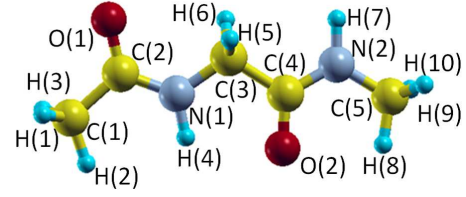


FIG. 2. Atomic structure of the glycine dipeptide molecule with atomic specification. Two dihedral angles, ϕ and ψ , are formed by the atomic series C(2)-N(1)-C(3)-C(4) and N(1)-C(3)-C(4)-N(2), respectively. The figure displays the atomic configuration with $(\phi, \psi) = (180^\circ, 180^\circ)$.

III. NUMERICAL DEMONSTRATION

A. Molecular configuration

To illustrate our *ab initio* approach to free energy reconstruction, we consider the free energy profile of glycine dipeptide molecule [2-(Acetylamino)-N-methylacetamide] in vacuum, as shown in Fig. 2. The atoms are specified by the symbol with numbering of C(1), C(2), ..., O(1), O(2), .. etc.. from the left-hand-side of the figure. The two dihedral angles are labeled as ϕ and ψ , which are formed by the atomic series C(2)-N(1)-C(3)-C(4) and N(1)-C(3)-C(4)-N(2), respectively. In other words, these angles are formed by the plane of N(1)-C(3)-C(4) and the plane associated with the peptide bond (-OCNH-). In nature, the latter plane in proteins has usually observed as the *trans*-form rather than as the *cis*-form.²¹ Actually, in our calculation, the *cis*-form of the right-hand-side of the peptide bonds in Fig. 2 is higher in energy by 2.1 kcal/mol than the form presented in Fig. 2.

In this section, we demonstrate the application of FP-LogMFD to the glycine dipeptide molecule. We have obtained the free energy landscape $F(\phi, \psi)$ with respect to the dihedral angles ϕ and ψ at room temperature 300 K ($= T_{\text{ext}}$). First, FP-LogMFD with the fixed dihedral angle ϕ was performed to set the parameters required and to obtain the one-dimensional free energy profile along ψ . Then, the FP-LogMFD runs in the ϕ - ψ space were performed, revealing the details of the two-dimensional free energy landscape. We have also performed TI calculation to reconstruct the one-dimensional free energy profile, which is compared to the FP-LogMFD result for benchmarking.

B. Parameter setting

For the CP-FPMD runs, we have used the plane wave basis set and density functional theory with the generalized gradient approximation(GGA).^{22,23} The energy cutoffs of 25 and 250 Ry are taken for electronic wave function and charge density, respectively.²⁴ The ultra-

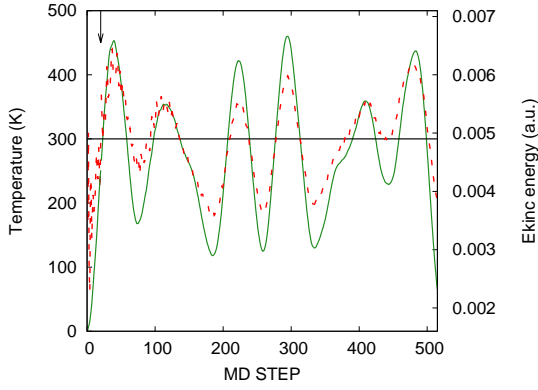


FIG. 3. Time evolution of the instantaneous temperature (green full curve, left scale) and the kinetic energy of the wave functions (red dashed curve, right scale) in the FPMD run at $T_{\text{ext}} = 300$ K with the constraints $\phi = -80.0^\circ$ and $\psi = -76.8^\circ$. The horizontal line indicates the values of T_{ext} and E_{kin}^0 . The arrow indicates the time step at which the constraint on the dihedral angles and the temperature control is turned on.

soft pseudopotentials are used.²⁵ The Γ -point sampling is adopted for the molecular system placed in a cubic box with the dimension of 20 a.u. (10.58 Å). For the canonical FPMD simulation in the framework of the BP method, the time step is set to 10 a.u. (~ 0.24 fs). This is a typical value for the CP method.¹³ The parameters for Q_R , Q_e , and m_ϕ are set to 5×10^5 a.u., 5×10^3 a.u.,²⁶ and 200 a.u.,²⁷ respectively. E_{kin}^0 in Eq. (13) is automatically determined by the ansatz described before (see Sec. II B). Figure 3 presents the time evolution of the kinetic energy of the wave functions and the instantaneous temperature of the molecular system (proportional to the kinetic energy of atoms). In the present calculations, E_{kin}^0 was set to be 0.0049 a.u.

In this demonstration, the following harmonic potentials are employed to constraint $\tilde{\phi}$ and $\tilde{\psi}$;

$$E_{\text{hp}} = \frac{1}{2}k_\phi(\tilde{\phi}(\{\mathbf{R}_I\}) - \phi)^2 + \frac{1}{2}k_\psi(\tilde{\psi}(\{\mathbf{R}_I\}) - \psi)^2 \quad (16)$$

where ϕ and ψ are the target dihedral angles [X_p in Eq. (12)] and $\tilde{\phi}$ and $\tilde{\psi}$ are the temporal ones determined from the instantaneous molecular configuration [\tilde{X}_p in Eq. (12)]. Both of k_ϕ and k_ψ are taken to be 2.4 a.u./rad² (0.46 kcal/mol/deg²). Figure 4 shows typical time evolution of $\tilde{\phi}$ and $\tilde{\psi}$ with $(\phi, \psi) = (-80.0^\circ, -76.8^\circ)$. This figure indicates that the temporal $\tilde{\phi}$ and $\tilde{\psi}$ fluctuate around the respective given value, implying the constraint to be imposed correctly.

The time evolution of the temporal force is presented in Fig. 5. Averaging over 500 steps (from the 21th step to 520th step), the mean forces acting on ϕ and ψ were estimated to be -0.06863 and 0.02220 (kcal/mol)/deg, respectively (the fluctuations are limited to ± 0.87 (kcal/mol)/deg). The accuracy of the MF strongly depends on the number of MD steps, defined as

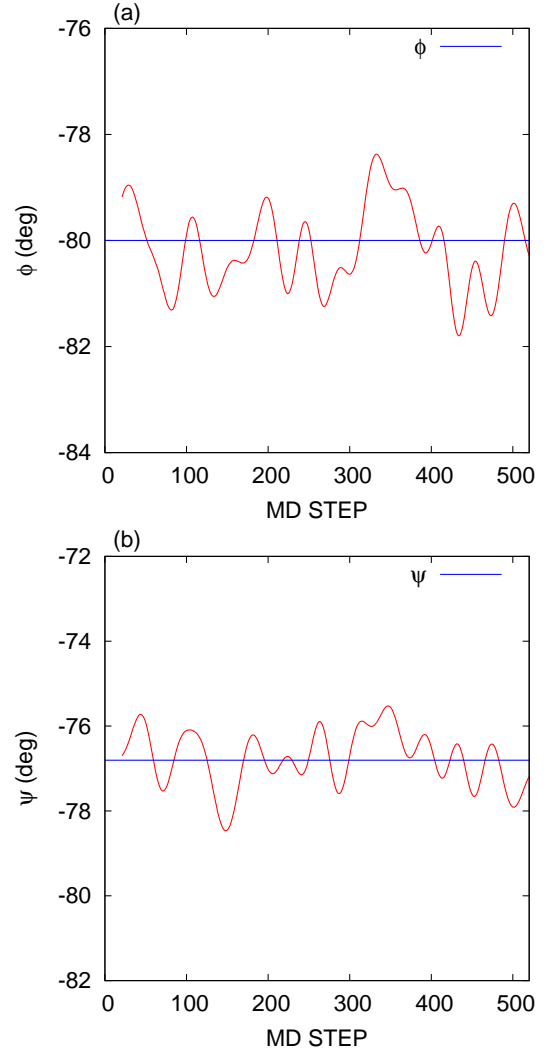


FIG. 4. Time evolution of the instantaneous dihedral angles, (a) $\tilde{\phi}$ and (b) $\tilde{\psi}$, in the FPMD run with the constraints, $\phi = -80.0^\circ$ and $\psi = -76.8^\circ$ (horizontal lines).

N_{BP} . In fact, we found that the decrease of N_{BP} (from 500 steps to 300 steps) deteriorated the MF, and the resultant free energy profile became much worse, compared to those by $N_{\text{BP}} = 500$. N_{BP} was thus set to 500 steps in the present study.

Evaluation of the MF is also needed in the TI method. The MF at each of the grid points in the TI calculation was obtained by averaging the instantaneous forces from a set of many FPMD runs with Eqs. (11) and (12). The successive simulation started with random atomic distortions from the previous atomic configuration. In the present study, we have performed 120 FPMD runs, each consisting of 600 FPMD steps, i.e., 72,000 FPMD steps in total for each grid point of the reaction coordinate. 60,000 FPMD steps out of the 72,000 steps were devoted to estimation of the MF at a single grid point.

For a set of given coordinates (ϕ, ψ) , as shown in Fig. 1, $-\partial F/\partial\phi$ and $-\partial F/\partial\psi$ were estimated for the hypotheti-

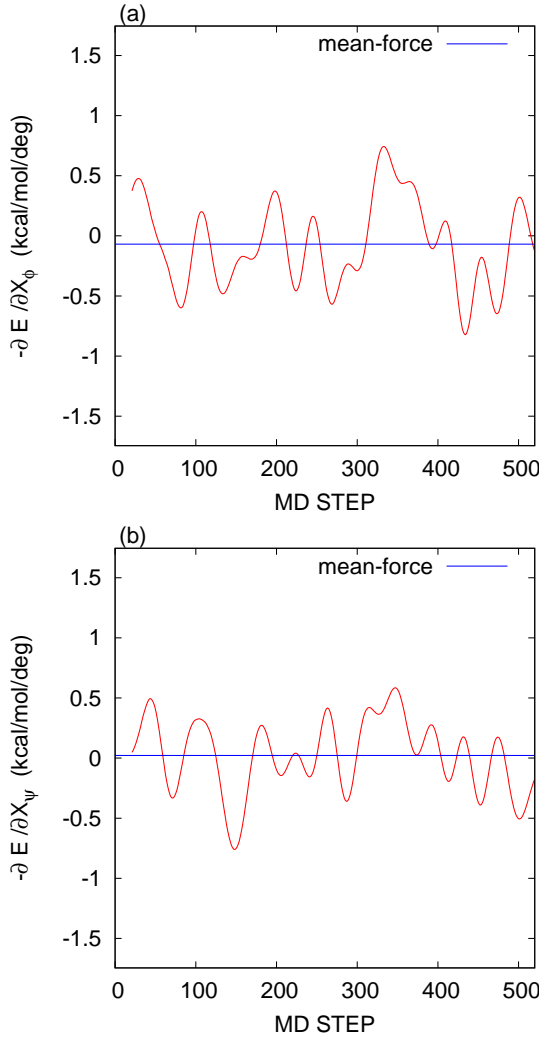


FIG. 5. Time evolution of the instantaneous force, (a) $k_\phi(\tilde{\phi} - \phi)$ and (b) $k_\psi(\tilde{\psi} - \psi)$, accompanied with the horizontal lines which indicates the mean forces, $-\partial F/\partial\phi$ and $-\partial F/\partial\psi$.

cal dynamics given by Eqs. (5) and (6) with $T_X = 300$ K in FP-LogMFD. A single Nosé-Hoover thermostat^{14,15,19} was used. In the FP-LogMFD runs, the variables of ϕ , ψ , and η were updated using a time step of 1τ , with the masses of $M_{\phi(\psi)} = 1.7 \times 10^4$ (kcal/mol)/(deg/ τ^2) and $Q_\eta = Lk_B T_X \tau_\eta^2$ with $\tau_\eta = 50\tau$, where τ represents the time unit. [the time unit can, in fact, be arbitrarily chosen, e.g., $\tau=1$ fs, since the dynamics of ϕ has nothing to do with the resultant $F(\phi)$.] The parameters of α and γ , which determines the degree of the effective reduction of the free energy barriers, were taken as $\alpha = 3$ (kcal/mol) $^{-1}$ and $\gamma = 1/\alpha$, with this value of γ corresponding to 170 K. After solving Eqs. (5) and (6), the conversion to $F(\phi, \psi)$ was performed using Eq. (10) with $\hat{H}_{\text{LogMFD}} = 1$ kcal/mol. \hat{H}_{LogMFD} should be set to ensure $\alpha F_{\min}(\phi, \psi) + 1 > 0$, where F_{\min} is the minimum of the free energy. Note however that there is, in principle, no upper limit for the value of \hat{H}_{LogMFD} .¹²

The validity of the LogMFD results mainly depends on the accuracy of the MF, which influences the conservation of \hat{H}_{LogMFD} [Eq. (7)]. As was already mentioned, the quality of the MF can be controlled by N_{BP} and the mass parameter $M_{\phi(\psi)}$.¹² The increase of $M_{\phi(\psi)}$, which reduces (suppresses) the velocity of the dynamical variables, results in a more accurate profile for the MF, and thus, the free energy profile. We found, by decreasing the $M_{\phi(\psi)}$ by the factor ten, that the difference between the LogMFD and TI results becomes 0.22 kcal/mol from 0.18 kcal/mol on average. In the present system, the periodicity with respect to ϕ and ψ can be available for checking the accuracy of simulations.

C. One dimensional profile

For demonstrating the free energy evaluation using FP-LogMFD, we performed FP-LogMFD simulations for the dynamical variable ψ while keeping ϕ to be -80° . In Fig. 6(a), the MF profiles from the LogMFD and TI calculations are presented, showing the LogMFD result is in good agreement with the TI result. Figure 6(a) also shows that there are regions where the MF drastically varies in a narrow range, e.g., $\psi = -115^\circ \sim -57.3^\circ$. In Fig. 6(b), the magnified profile in the range of $-78.5^\circ \leq \psi \leq -74.9^\circ$ indicates that, although the data by LogMFD shows a vibrational behavior, the MF averaged over 10 MFD steps varies smoothly. This behavior of the MF in LogMFD is remarkable when the profile exhibits a rapid variation. As shown in Fig. 6(b), a set of uniformly sparse grid points is only used in the TI method due to a limited computational resources. LogMFD thus can provide missing data in between each of the grid points in the TI calculations without much additional computational cost.

Figure 7 shows the free energy profiles obtained by the LogMFD and TI methods. Each of the free energy profiles is shifted to have the same value (5 kcal/mol) at $\psi = -180^\circ$ for comparison in Fig. 7. LogMFD runs were initiated at $\psi = 57.3^\circ$ (around the minimum) to either direction (with increasing or decreasing ψ) with $T_X = 300$ K and were ended at $\psi = 92^\circ$ after passing through the periodic boundary at 180° or -180° . It should be remarked that the value of $F(\psi = 92^\circ)$ estimated when $\psi = 92^\circ$ was sampled for the first time is almost the same as the $F(\psi = 92^\circ)$ estimated when $\psi = 92^\circ$ was sampled the second time, indicating the energy dissipation, which degrades the accuracy of $F(\psi)$, is negligible.

There is the maximum at $\psi = -77.9^\circ$, and the minimum at $\psi = 63.0^\circ$ in the profile, as shown in Fig. 7. We stress here that the dynamics for the reaction coordinate ψ was very smooth, even the large energy barrier exists. The difference between the minimum and maximum free energy approximately amounts to 8 kcal/mol, corresponding to about 4024 K. This energy difference was entirely suppressed by the logarithmic form. Figure 7 also shows the effective potential curve of $\gamma \log(\alpha F(\psi) + 1)$,

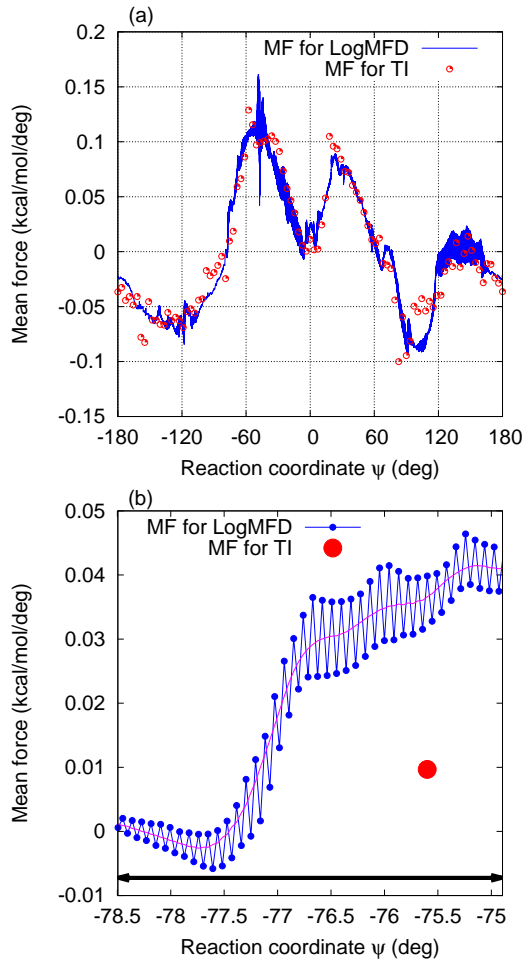


FIG. 6. (a) MF with respect to the dihedral angle ψ in the glycine dipeptide molecule, constraining the other dihedral angle ϕ to -80° . The blue curve and red symbols indicate the MF calculated from the LogMFD and TI calculations, respectively. (b) The magnified profile of the MF (vibrational curve) around $\psi = -76.8^\circ$, with a smooth curve showing the profile obtained by averaging over ten MFD time steps. The arrow indicates the width of the mesh used in the TI calculation, showing that the MF around this ψ range is approximated by only a single grid-point result.

indicating that the actual energy barrier for ψ became ~ 0.8 kcal/mol, comparable to 402 K. Such a substantial reduction of the energy barrier can be controlled by the parameters (α and γ).

Before proceeding to the two dimensional landscape, we discuss the one-dimensional free energy profile in more detail. As pointed out, there are the minimum and maximum in the profile. The former and latter are related to a hydrogen bond and a rendezvous of a pair of the oxygen atoms in the peptide bonds, respectively. Other characteristic properties are found around $\psi = 0^\circ$ and 140° , where the free energy shows a profile with zero curvature. We consider that this is due to breaking of the hydrogen bond which is formed around $\psi = 57.3^\circ$. This consideration is supported by the fact that the MF in the

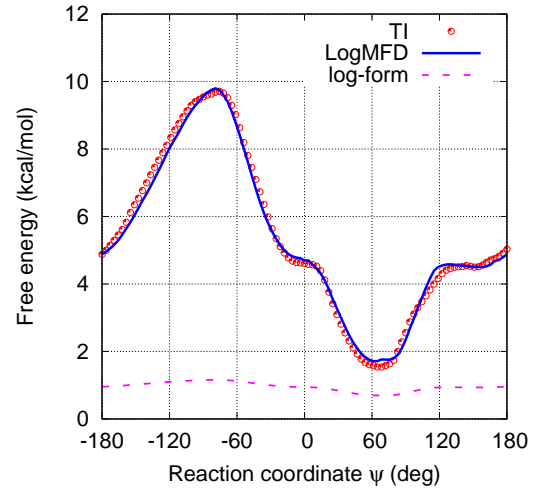


FIG. 7. Free energy profiles with respect to the dihedral angle ψ in the glycine dipeptide molecule, constraining the other dihedral angle ϕ to -80° , obtained from the LogMFD (blue curve) and TI (red dots) calculations. The logarithmic energy ($\gamma \log(\alpha F(\psi) + 1)$) (magenta curve) is also presented for comparison, indicating a substantial reduction of the free energy barrier.

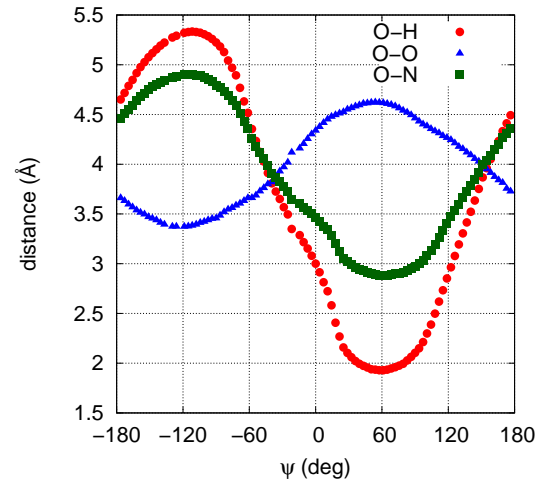


FIG. 8. Atomic distances for O(1)-H(7), O(1)-O(2), and O(1)-N(2) as a function of ψ .

corresponding part is almost zero (see Fig. 6). Atomic distances as a function of ψ are shown in Fig. 8. From this figure, the free energy minimum in Fig. 7 is found to appear around the minimum distance of O(1)-H(7) and O(1)-N(2), while the energy maximum appears around the minimum distance of O(1)-O(2). The latter case may correspond to a large electric dipole state for the molecule. The distance of $2.5 \sim 3$ Å for O(1)-H(7) at $\psi = 0^\circ$ and 120° is out of the range of the hydrogen bonding, where the MF is ~ 0 . From this, we consider that an energy of about 3 kcal/mol is gained by the hydrogen bond (see Fig. 7). This energy is comparable to

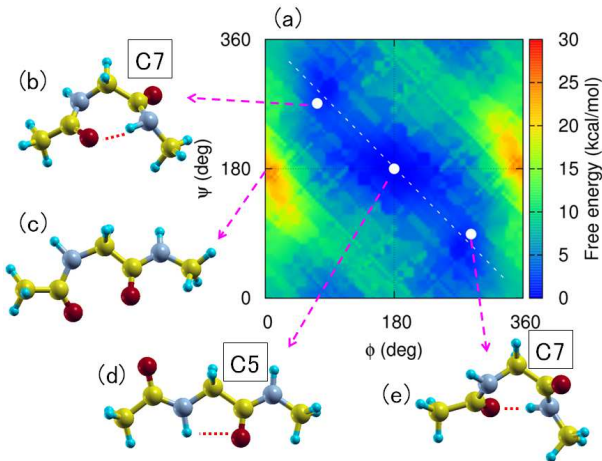


FIG. 9. (a) Free energy contour map $F(\phi, \psi)$ and (b)–(e) typical atomic configurations at three stable states (C5 and C7 atomic configurations) and an unstable state. The white bullets indicate the positions for the stable states. A pass way that approximately connects these stable states with a straight line is displayed in a white dashed line (see also Fig. 10).

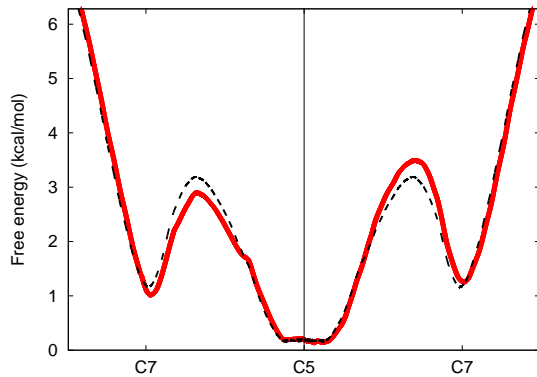


FIG. 10. The one dimensional free energy profile along the line that approximately connects the C5 and C7 states. The full and dotted curves represents the bare and symmetrized plot of $F(\phi, \psi)$.

a typical bonding energy of the hydrogen bond ($3 \sim 10$ kcal/mol) reported in a literature.²¹

D. Two dimensional profile

For constructing the two dimensional free energy profile, the dynamical equations for both of ϕ and ψ were used. Supposing that the free energy minimum in the ϕ - ψ space may be lower than that in the one-dimensional ψ space at $\phi = -80^\circ$, \hat{H}_{LogMFD} was increased to 1.2 kcal/mol to shift the baseline of the free energy landscape. The temperature T_X and α were chosen to be small values; $T_X = 200$ K and $\alpha = 2$ (kcal/mol)⁻¹ to

suppress numerical errors in longer simulations, while the other parameters took the same values as used in the one dimensional FP-LogMFD calculations. The two-dimensional FP-LogMFD runs were started from the minimum of the one dimensional profile of $F(\psi)$ and were extended to four directions. The branch off can be performed from one simulation to others. These simulations can be performed independently, implying that parallel treatment is highly effective in LogMFD.¹²

Figure 9 shows the free energy contour map in the ϕ - ψ plane with typical molecular configurations. The glycine dipeptide molecule has an intrinsic mirror symmetry in its atomic geometry. Atomic structures which are related to each other by the mirror operation with respect to the N(1)-C(3)-C(4) plane has the same energy in gas phase. This feature should also be seen in the free energy landscape $F(\phi, \psi)$. Therefore, the statistical errors can be reduced by symmetrizing the two-dimensional free energy with respect to the point of $(\phi, \psi) = (180^\circ, 180^\circ)$ (there is the inversion symmetry in the map). A non-symmetrized free energy profile along the white dashed line in Fig. 9 is presented in the last paragraph in this subsection.

The free energy landscape (Fig. 9) shows that there are three stable states (three energy valleys) and a series of unstable states (energy mountains). The most stable state appears around $(\phi, \psi) = (180^\circ, 180^\circ)$, whose atomic configuration is presented in Fig. 2 (or Fig. 9(d)). This is assigned to the C5 configuration²⁸ and is stabilized by the hydrogen bond, the five-membered ring, and the configuration with separated oxygen atoms (almost zero electric dipole). The other two stable states, found around $(\phi, \psi) = (288^\circ, 88^\circ), (72^\circ, 272^\circ)$, are assigned to the C7 configuration and are also stabilized with the hydrogen bond, the seven-membered ring, and the configuration with moderately separated oxygen atoms (small electric dipole). The free energy for the C7 configuration is higher by 0.58 kcal/mol than that for the C5 configuration. This energy difference is quite small and comparable to 290 K. The total (internal) energy computation also indicates that the C5 configuration is either lower in energy than the C7 by 0.38 kcal/mol, while the work by the quantum chemistry calculation reports that the C5 is either lower than the C7 by 0.58 kcal/mol,²⁹ or higher by 1 and 0.58 kcal/mol.^{30,31} The atomic configuration of the most unstable state is presented in Fig. 9(b). This instability comes from an assemble of oxygen atoms in the molecule (implying a large electric dipole). The energy barrier measured from the bottom of the free energy landscape (highest energy mountain) amounts to 26 kcal/mol, corresponding to 13000 K and to 730 K with $\gamma \log(\alpha F + 1)$. Again, LogMFD enables to sample such higher energy configuration in the same footing used around the ground state.

It is interesting to see the transition from the most stable state to another stable state. The one dimensional free energy profile roughly linking the C7 and C5 configurations is presented in Fig. 10, as a typical energy

profile. For simplicity, the pass way of reaction coordinate was assumed to be along the straight line which connects the two states near the C5 and C7 states in the ϕ - ψ plane, as specified in Fig. 9. From Fig. 10, the energy barrier between C5 and C7 configurations is estimated to be about 3 kcal/mol when measured from the C5 configuration. The energy differences between the C5 and C7 states shown in Fig. 10 are about 1 kcal/mol. These values are slightly larger than the value reported above (0.58 kcal/mol) because of the approximate pass way (this approximation causes the uncertainty of about 0.4 kcal/mol).

E. Computational efficiency

In constructing the free energy profile (Fig. 7), 4×10^6 FPMD steps were devoted in the FP-LogMFD calculation, while 7.2×10^6 FPMD steps were needed in the TI calculation. About 45 % of the computational cost was saved. This demonstrates a good efficiency of LogMFD in the computational cost. In addition, in the course of the construction of the two dimensional profile (Fig. 9), we carried out a set of LogMFD runs which, in total, sampled 1.2×10^8 FPMD steps (configurations). Even though the accuracy in the two dimensional profile may be slightly reduced, the computational cost is only 30 times larger than that in the one dimensional calculation.

IV. DISCUSSIONS

As mentioned in Sec. III A, the peptide bond takes the *trans*- or *cis*-form. In our simulations, the *trans*-form has been entirely observed and the statistical sampling of the *cis*-form has been missed. This is because the barrier between the *trans*- and *cis*-forms may be extremely high, and also because the reaction coordinates chosen in the present LogMFD calculations may not be suitable for sampling the *cis*-form. If one needs to sample the *cis*-form, incorporation of additional reaction coordinates is of use, which is easily realized in LogMFD.

It is interesting to see the contribution of the entropy in the free energy. We have calculated the total energy (the internal energy) as a function of ψ keeping $\phi = -80^\circ$, as shown in Fig. 11. The grid points used in the calculation of the internal energy are the same as used in the TI calculation. The internal energy profile is very similar to the free energy profile (Fig. 7). The difference between the free energy and the internal energy is found to be within 0.5 kcal/mol (if the energy scale is adjusted to give zero entropy at $\psi = -180^\circ$), implying a small contribution from the entropy. We roughly estimated the uncertainty of the free energy as ~ 0.4 kcal/mol, which is comparable to the variation of the entropy with ψ . It is thus considered that the entropic contribution is hardly changed with ψ . This is not surprising because the num-

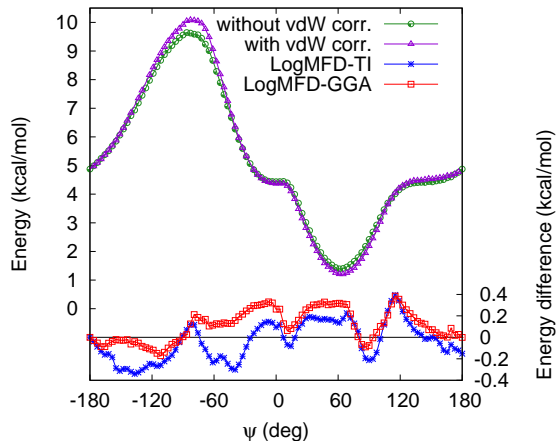


FIG. 11. Total (internal) energy for the glycine dipeptide molecule as a function of ψ keeping $\phi = -80^\circ$, which was obtained from the density functional theory (DFT) calculation with (purple triangle symbols) or without (green circle symbols) the van der Waals(vdW) correction. The blue asterisks denote the difference between the free energy obtained by LogMFD and that by TI, while the red squares denote the difference between the free energy by LogMFD and the internal energy without the vdW correction.

ber of possible conformations in the present system is relatively small, which does not significantly depend on the dihedral angles. Also, the glycine dipeptide molecule is in vacuum, not in a solvent. We however stress that LogMFD is able to unveil the variation of the entropy, if any, which is, for example, seen in our preliminary calculations for a model system of protein-G consisting of 56 amino acids.³²

The free energy profile for the glycine dipeptide molecule was previously obtained using classical LogMFD with an empirical force field.^{11,12} The profile is similar to that obtained using FP-LogMFD in this work, indicating the validity of the empirical force-field to some extent. There are, however, some differences in the profile. As pointed out in Sec. III C, we observe the zero curvature around $\psi = 0^\circ$ and 140° . This behavior is also seen in the internal energy profiles (Fig. 11) in the FP-LogMFD approach. In fact, the explicit inclusion of the van der Waals interaction³³⁻³⁵ into the DFT(GGA) calculations does not change the overall profile of the internal energy (note that the binding energy is underestimated using GGA). It is thus considered that the zero curvature is not attributed to an inappropriate DFT description, while the linear behavior observed around $\psi = 0^\circ$ and 140° in the previous results may come from insufficient transferability of the empirical force field.

V. SUMMARY

We have demonstrated that the *ab initio* based MF can be incorporated into the LogMFD method, which

improves the reliability and accuracy in the free energy calculation. FP-LogMFD has been applied to reconstruction of the free energy landscapes of the glycine dipeptide molecule, and the C5 and C7 conformations have been identified as the ground and metastable conformations, respectively. It has been confirmed that the substantial reduction of the free energy barriers, thanks to the logarithmic form, enables us to efficiently reconstruct the free energy profile, which was found to agree well with that obtained by the TI method. The free energy profile from the first-principles approach indicates that the empirical force field for the glycine dipeptide molecule is sufficient to obtain the overall profile of the free energy landscape.

The LogMFD method allows us not only to easily sample rare events, but also to reconstruct the free energy profile “*on-the-fly*” without suffering from the problems such as how to arrange the grid points or how to perform the numerical integration (as postprocessing) in TI. It has been demonstrated in the present study that free energy profiles using *ab initio* force field can be reconstructed with less computational cost than is needed in the TI method. The FP-LogMFD method developed here is thus a promising tool for reconstructing free energy profiles, especially those in which accurate descriptions for interatomic interactions are required.

ACKNOWLEDGMENTS

The computation in this work was done using the facilities of the Supercomputer Center, Institute for Solid State Physics, University of Tokyo and the facilities of the Research Center for Computational Science, National Institutes of Natural Sciences, Okazaki, Japan. This work was partly supported by Grant-in-Aid for Scientific Research from JSPS/MEXT (Grant Nos. 22104012, 22340106, 23510120 and 24740297) and the Computational Materials Science Initiative (CMSI), Japan.

Appendix A: Thermodynamic integration

In order to check the result of the LogMFD calculations, thermodynamic integration (TI) was also performed for comparison using the same computational conditions for the first-principles MD calculations (see Sec. III B). When one carries out a long-time CP-FPMD simulation, the energy tends to flow to the electronic degrees of freedom from the ionic degrees of freedom. Consequently, the lift from the BO surface of the electronic wave functions becomes obvious, and finally, the simulation may break down.³⁶ However, one can, instead, perform multiple short FPMD runs and the mean force profile in the TI calculation can be constructed by averaging over the configurations from all of these short runs at a given set of ϕ and ψ . Figure 12 represents the convergence behavior of the MF with several fixed ψ , as a function of the number of statistical samplings. From

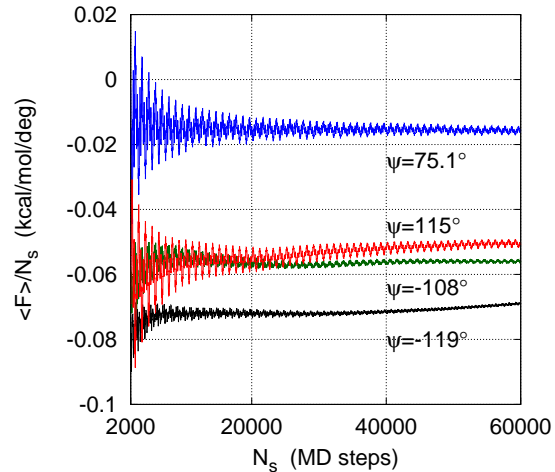


FIG. 12. Cumulative averages of the mean force in the TI calculation for several dihedral angles ($\psi = -119^\circ, -108^\circ, 75.1^\circ, 115^\circ$) under the condition $\phi = -80^\circ$.

this result, we decided to use 60,000 FPMD steps in total to estimate the MF at each grid point of ψ in our TI calculation.

- ¹Y. Yamamori and A. Kitao, J. Chem. Phys. **139**, 145105 (2013).
- ²W. Sinko, C. A. F. de Oliveira, L. C. T. Pierce, and J. A. McCammon, J. Chem. Theory Comput. **8**, 17 (2012).
- ³G. König, P. S. Hudson, S. Boresch, and H. L. Woodcock, J. Chem. Theory Comput. **10**, 1406 (2014).
- ⁴G. Ciccotti and M. Ferrario, Mol. Simul. **30**, 787 (2004).
- ⁵M. Sprik and G. Ciccotti, J. Chem. Phys. **109**, 7737 (1998).
- ⁶J. G. Kirkwood, J. Chem. Phys. **3**, 300 (1935).
- ⁷R. W. Zwanzig, J. Chem. Phys. **22**, 1420 (1954).
- ⁸G. M. Torrie and J. P. Valleau, J. Comput. Phys. **23**, 187 (1977).
- ⁹L. Rosso, P. Mináry, Z. Zhu, and M. E. Tuckerman, J. Chem. Phys. **116**, 4389 (2002).
- ¹⁰A. Laio and M. Parrinello, Proc. Natl. Acad. Sci. USA **99**, 12562 (2002); A. Laio and F. L. Gervasio, Rep. Prog. Phys. **71**, 126601 (2008).
- ¹¹T. Morishita, S. G. Itoh, H. Okumura, and M. Mikami, Phys. Rev. E **85**, 066702 (2012).
- ¹²T. Morishita, S. G. Itoh, H. Okumura, and M. Mikami, J. Comput. Chem. **34**, 1375 (2013).
- ¹³R. Car and M. Parrinello, Phys. Rev. Lett. **55**, 2471 (1985).
- ¹⁴S. Nosé, Mol. Phys. **52**, 255 (1984).
- ¹⁵W. G. Hoover, Phys. Rev. A **31**, 1695 (1985).
- ¹⁶P. E. Blöchl and M. Parrinello, Phys. Rev. B **45**, 9413 (1992).
- ¹⁷T. Morishita and S. Nosé, Phys. Rev. B **59**, 15126 (1999).
- ¹⁸J. P. Ryckaert, G. Ciccotti, and H. J. C. Berendsen, J. Comput. Phys. **23**, 327 (1977).
- ¹⁹T. Morishita, Mol. Phys. **108**, 1337 (2010); The version of $L = 1$ in this reference was used.
- ²⁰M. C. Payne, M. P. Teter, D. C. Allan, T. A. Arias, and J. D. Joannopoulos, Rev. Mod. Phys. **64**, 1045 (1992).
- ²¹D. Voet and J. G. Voet, *Biochemistry* (J. Wiley, USA, 4th edit., 2011).
- ²²W. Kohn and L. J. Sham, Phys. Rev. A **140**, 1133 (1965).
- ²³J. P. Perdew, J. A. Chevary, S. H. Vosko, K. A. Jackson, M. R. Pederson, D. J. Singh, and C. Fiolhais, Phys. Rev. B **46**, 6671 (1992).
- ²⁴A. Pasquarello, K. Laasonen, R. Car, C. Lee, and D. Vanderbilt, Phys. Rev. Lett. **69**, 1982 (1992); K. Laasonen, A. Pasquarello,

- R. Car, C. Lee, and D. Vanderbilt, Phys. Rev. B **47**, 10142 (1993).
- ²⁵D. Vanderbilt, Phys. Rev. B **41**, 7892 (1990).
- ²⁶T. Oda, J. Phys. Soc. Jpn. **71**, 519 (2002).
- ²⁷T. Oda and A. Pasquarello, Phys. Rev. B **70**, 134402 (2004).
- ²⁸T. C. Cheam and S. Krimm, J. of Mol. Struct., **193**, 1 (1989).
- ²⁹D. Q. McDonald and W. C. Still, Tetrahedron Lett. **33**, 7743 (1992).
- ³⁰H. Fujitani, A. Matsuura, H. Sato, and Y. Tanida, J. Chem. Theory Comput. **5** 1155 (2009).
- ³¹V. J. Klimkowski, L. Schäfer, F. A. Momany, and C. V. Alsenoy, J. of Mol. Struct., **124**, 143 (1985).
- ³²M. Isobe, H. Shimizu, and Y. Hiwatari, J. Phys. Soc. Jpn., **70**, 1233 (2001).
- ³³M. Dion, H. Rydberg, E. Schröder, D. C. Langreth, and B. I. Lundqvist, Phys. Rev. Lett. **92**, 246401 (2004) [Erratum **95** 109902(E) (2005)].
- ³⁴V. R. Cooper, Phys. Rev. B **81**, 161104(R) (2010).
- ³⁵M. Obata, M. Nakamura, I. Hamada, and T. Oda, J. Phys. Soc. Jpn. **82**, 093701 (2013).
- ³⁶G. Pastore, E. Smargiassi and F. Buda, Phys. Rev. A **44**, 6334 (1991).